# Reduction in Functional Antibody Activity Against *Streptococcus pneumoniae* in Vaccinated Elderly Individuals Highly Correlates with Decreased IgG Antibody Avidity

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The pneumococcal polysaccharide vaccine is recommended as a means of preventing invasive disease in the elderly. We compared responses to the 23-valent polysaccharide vaccine in 46 previously unvaccinated, healthy, institutionalized elderly persons (mean age, 85.5 years) with those in 12 healthy younger adults (mean age, 37 years) by measuring prevaccination and postvaccination serum IgG antibody concentrations (by ELISA), functional antibody activity (by opsonophagocytosis), IgG antibody avidity, and passive protection in mice. Postvaccination IgG antibody concentrations for two serotypes (6B and 19F) of the five studied (4, 6B, 14, 19F, and 23F) were significantly lower in elderly than in younger adults; however, opsonophagocytic activity was significantly reduced for all serotypes in the elderly. Sera with reduced opsonophagocytic activity (titer, <64) correlated with low IgG antibody avidity and protected mice poorly against pneumococcal challenge. In elderly persons receiving polysaccharide vaccination, there was a significant reduction in the functionality of postvaccination antibodies, and this appeared to increase with advanced age.

*Streptococcus pneumoniae* is one of the leading causes of community-acquired pneumoniae and is associated with high morbidity and mortality among the elderly [1–3]. Elderly persons are at increased risk for pneumococcal pneumonia and bacteremia [1, 4, 5]. Vaccination with the 23-valent pneumococcal polysaccharide vaccine is recommended for persons ≥65 years of age, regardless of their immunocompetence status. To date, less than one-third of the eligible elderly population has been vaccinated [4, 6]. The estimated efficacy of pneumococcal vaccine in immunocompetent elderly persons (age range, 65–75 years) is 70%–78% [7, 8], and in all elderly persons, 44%–61% [9]. Although studies have provided data about the general efficacy of the vaccine, more accurate surrogates of protection are needed to evaluate immune status in the elderly after vaccination and to assist in developing recommendations for revaccination [4, 10].

See editorial response by Janoff and Rubins on pages 289–91.

The immune response to the polysaccharide vaccine in various age groups, including the elderly, has been studied previously [11–17]. Concentrations of antibody to pneumococcal capsular polysaccharides (PPSs) found in the elderly generally are thought to be similar to those in younger adults [12–14], although responses to certain polysaccharides may be reduced, with a more marked reduction in persons >85 years of age [14, 18]. In addition, elderly women may have lower responses than elderly men [14]. Data suggest that the protective effect of the pneumococcal vaccine diminishes with age [19]. A possible explanation is that anticapsular IgG antibodies of elderly persons may not be as effective in opsonizing pneumococci for phagocytosis. Studies of the functionality of the antibodies elicited by the 23-valent polysaccharide vaccine in older subjects [20] are very limited in number.

In the present study, titers of IgG antibody to PPSs and opsonophagocytic titers were determined prior to and following vaccination of institutionalized elderly persons and were compared with those in younger adult controls. In addition, antibody avidity and passive protection in mice were studied with use of selected sera from elderly persons who had high IgG antibody concentrations and low opsonophagocytic titers. This study contributes to the understanding of the immune response in elderly persons to the 23-valent pneumococcal

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polysaccharide vaccine and presents opsonophagocytosis as an immune status indicator that should be included in assessment of the immune response of elderly persons to polysaccharide vaccination.

## Materials and Methods

*Study group, vaccination, and sera collection.* Forty-six elderly residents of a nursing home in Chicopee, Massachusetts, were vaccinated with the licensed 23-valent polysaccharide vaccine (Pnu-Immune 23; Lederle-Praxis-American Cyanamid, Pearl River, NY) as part of an epidemiological investigation of an outbreak of pneumonia in which parainfluenza virus and *S. pneumoniae* serotype 14 were implicated [21]. A dose of vaccine contained 25 $\mu$g of each of 23 pneumococcal polysaccharide types.

Ages of the elderly subjects ranged from 63 to 103 years (mean, 85.5 years); 39 were female and seven were male. The study group was stratified into three age groups: group 1, 63 through 79 years ($n$ = 10); group 2, 80 through 89 years ($n$ = 22); and group 3, $\geq$90 years ($n$ = 14). Because the study population was primarily female, it was not stratified by gender. Paired sera were collected from all study participants. Sera designated as "pre" were collected within 3 days of vaccination; sera designated as "post" were collected 2–3 weeks following vaccination. Sera were stored at $-70$°C until tested. All participants were healthy at the time of vaccination; none was bedridden.

*Control group.* Twelve healthy younger adults (aged 22–46 years; mean age, 37.0 years)—an equal number of men and women—were used as controls. Paired sera obtained prior to and 4 weeks following vaccination with the Pnu-Immune 23 were collected and stored at $-70$°C.

*ELISA IgG antibody concentrations.* IgG antibody concentrations to PPSs from *S. pneumoniae* serotypes 4, 6B, 14, 19F, and 23F (abbreviated as PPS 4, PPS 6B, PPS 14, PPS 19F, and PPS 23F) were measured by a modified ELISA [22]. These serotypes are commonly isolated from patients with invasive disease and are associated with an increase in the frequency of resistance to drugs [3]. The 89SF standard reference serum (U.S. Food and Drug Administration, Bethesda, MD) was used to calculate serum antibody concentrations in micrograms per milliliter. Absorption of serum antibodies to the common cell-wall polysaccharide (CPS) was performed by incubation (for 30 minutes at room temperature) of diluted serum (1:50) in a solution of purified CPS (10 $\mu$g/mL; Statens Seruminstitut, Copenhagen). The substrate used was *o*-phenylenediamine dihydrochloride (Sigma, St. Louis).

*Opsonophagocytosis.* Functional antibody activity was measured in prevaccination and postvaccination sera by opsonophagocytosis (an antibody- and complement-dependent reaction), with use of differentiated HL-60 cells (granulocytes) as the effector cells [23]. HL-60 granulocytes can efficiently phagocytize and kill pneumococci, giving opsonophagocytic titers that highly correlate with those obtained with polymorphonuclear neutrophils from donors [23]. Opsonophagocytic titers were calculated for pneumococcal serotypes 4, 6B, 14, 19F, and 23F in a viability assay as the reciprocal of the serum dilution that had $\geq$50% killing by differentiated HL-60 cells, in comparison with antibody-free complement-rich controls (12.5% per well of 3- to 4-week rabbit serum; Pel-Freez, Brown Deer, WI). All pneumococcal strains used in this study were recent clinical isolates previously used as reference strains [23].

*Antibody avidity determinations.* The relative functional antibody avidity of selected postvaccination sera from elderly and younger adults with anticapsular IgG concentrations greater than or equal to a threshold concentration of 2 $\mu$g/mL and decreased functional antibody activity (below a threshold titer of 64) was compared with the avidity in postvaccination sera with ELISA levels of $\geq$2 $\mu$g/mL and functional activity of $\geq$64 in opsonophagocytic titers. Antibody avidity measures the relative strength of the antigen-antibody binding. Antibody avidity can affect the measurement of ELISA IgG concentrations used in the evaluation of vaccine-induced antibodies [24, 25].

Relative antibody avidity was determined by a modification of the method previously described by MacDonald et al. [26]. In brief, Immulon IV (Dynatech, Alexandria, Va) microtiter plates were coated with 10 $\mu$g/mL of each polysaccharide tested. A single predetermined serum concentration (from the linear portion of each serum ELISA IgG curve) was loaded onto each well in a 50-$\mu$L volume. Subsequently, 50 $\mu$L of a series of seven threefold dilutions of sodium thiocyanate (NaSCN; Sigma), a chaotropic compound that interferes with the antigen-antibody reaction, was added to each well, so that the final concentration ranged from 4 $M$ to 0.05 $M$. Addition of NaSCN solution to the PPS-coated plates did not affect the amount of PPS bound to the plate. Plates were incubated at 37°C for 2 hours. The remainder of the assay was done following the antipneumococcal IgG-specific ELISA described above. The percentage reduction of the total absorbance (wave length, 460 nm) was calculated for each NaSCN concentration.

*Passive protection in mice.* The capacity of serum to passively protect mice against challenge with *S. pneumoniae* serogroup 4 was investigated in an adult mouse model with death as an endpoint [27]. Bacterial challenges were performed in groups of four outbred Swiss White mice (6–8 weeks old) with 10, 100, and 1,000 times the $LD_{50}$, 45 minutes after intraperitoneal injection of 0, 6, 18, 50, or 150 ng of IgG obtained by diluting the human sera to yield the desired dose in a final volume of 0.1 mL. One $LD_{50}$ corresponded to 2–4 bacteria/mL. The number of surviving mice was recorded at 5 days after challenge.

*Statistical analysis.* Linear correlations were calculated with use of the Pearson's product moment correlation coefficient. Differences among groups of data were determined by

the Mann-Whitney rank-sum test, and those between pairs in 2-by-2 tables were determined by a two-tailed Fisher's exact test. Significance level was set at $P < .05$ for all tests. The opsonophagocytic titers and ELISA IgG antibody concentrations (µg/mL) were converted to a $\log_2$ base for statistical analysis. Opsonophagocytic titers <8 were reported as titers of 4 for calculation purposes. Single antibody avidity values were calculated as the weighted average of the NaSCN concentration able to reduce most of the ELISA IgG absorbance. Weights were assigned as the percent reduction of total absorbance for each serum at each NaSCN concentration. Statistical calculations were performed with use of SigmaStat software, version 1.0 (Jandel, San Rafael, CA), and Epi Info software, version 6.02 (Centers for Disease Control, Atlanta).

## Results

*IgG antibody detected by ELISA.* Following vaccination, elderly subjects had significant increases in concentrations of IgG antibody to all serotypes tested. Comparison of the postvaccination IgG antibody concentrations of elderly adults with those of young adults revealed differences in the responses by age group. Table 1 gives the geometric mean concentrations (GMCs) of IgG and opsonophagocytic geometric mean titers (GMTs) for younger and elderly adults. IgG antibody GMCs in the elderly for serotypes 6B and 19F (GMCs of 5.1 and 5.8 µg/mL, respectively) were significantly lower than those in the young adult group (10.1 and 14.0 µg/mL, respectively).

**Table 1.** Geometric mean IgG PPS-specific serum antibody concentrations (µg/mL, per ELISA) and opsonophagocytic titers (reciprocal serum dilution) for elderly and young recipients of 23-valent pneumococcal polysaccharide vaccine.

| | | Value determined by indicated method, per age group | | | |
|---|---|---|---|---|---|
| | | Young controls, aged 22–46 y ($n$ = 12) | | All elderly subjects, aged 63–103 y ($n$ = 46) | |
| *Streptococcus pneumoniae* serotype | Serum specimen | ELISA | Opsono | ELISA | Opsono |
| 4 | Pre | 0.8 | 10.4 | 0.8 | 5.2* |
| | Post | 2.6 | 152.2 | 1.7 | 24.6* |
| 6B | Pre | 3.7 | 25.3 | 2.5 | 5.5* |
| | Post | 10.1 | 352.1 | 5.1* | 37.3* |
| 14 | Pre | 0.8 | 19.0 | 2.6* | 9.3* |
| | Post | 10.0 | 304.4 | 10.0 | 76.6* |
| 19F | Pre | 5.2 | 20.1 | 2.9 | 7.1* |
| | Post | 14.0 | 152.2 | 5.8* | 28.7* |
| 23F | Pre | 2.6 | 7.5 | 2.5 | 7.9 |
| | Post | 6.2 | 71.5 | 4.8 | 22.0* |

NOTE. Opsono = opsonophagocytosis; Post = postvaccination; PPS = pneumococcal capsular polysaccharide; Pre = prevaccination.

* Significant difference ($P < .05$) vs. values for the younger controls, by the Wilcoxon sample test (the Mann-Whitney rank-sum test was in agreement for the comparison between all younger adults and all elderly recipients for both ELISA IgG concentration and opsonophagocytic titer).

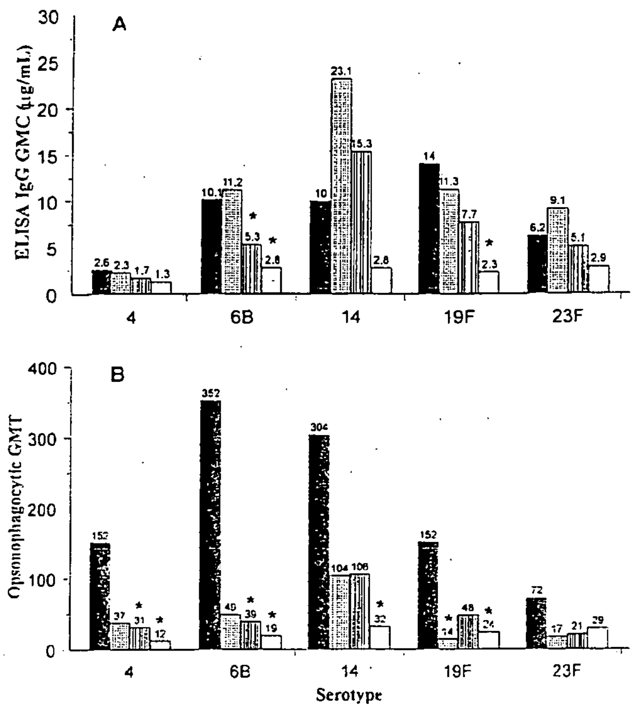


**Figure 1.** *A,* Geometric mean concentration (GMC; µg/mL) of IgG pneumococcal capsular polysaccharide–specific serum antibody, as determined by ELISA, for young controls (22–46 years; $n$ = 12; *black bars*) and for elderly age groups 1 (63–79 years; $n$ = 10; *dotted bars*), 2 (80–89 years; $n$ = 22; *striped bars*), and 3 (≥90 years; $n$ = 14; *open bars*) following vaccination with the 23-valent pneumococcal polysaccharide vaccine. *B,* Geometric mean opsonophagocytic titer (GMT; reciprocal serum dilution) for the young controls and elderly age groups shown in panel *A*, following vaccination. An asterisk designates a significant difference ($P < .05$) from values for the younger controls, per the Wilcoxon sample test.

Other significant differences in IgG concentrations in elderly and young adults following vaccination included lower GMCs against serotype 6B in elderly groups 2 and 3 (5.3 µg/mL and 2.8 µg/mL, respectively, vs. 10.1 µg/mL in young adults) and against serotype 19F in elderly group 3 (2.3 µg/mL, vs. 14.0 µg/mL in young adults) (figure 1A). Prevaccination ELISA IgG antibody concentrations were significantly different for serotype 14, when those in all elderly recipients were compared with those in younger adults.

The percentage of vaccinees attaining a twofold or higher rise in IgG antibody concentration was lower in the elderly than in young adults for serotypes 6B and 14 (table 2). However, no difference was observed in the numbers of elderly vs. young adult subjects with an IgG antibody concentration of ≥2 µg/mL following vaccination, except for serotype 19F (9 of 14 in elderly group 3 [age, ≥90 years] vs. 12 of 12 young adults).

*Opsonophagocytic antibody activity.* Far more striking than the IgG antibody differences given above were the significant reductions in postvaccination opsonophagocytic GMTs for the elderly vs. young adults. For all serotypes tested, there

**Table 2.** Percentage of elderly and young recipients of 23-valent pneumococcal polysaccharide vaccine with a twofold or higher rise in ELISA IgG concentration or a fourfold or higher rise in opsonophagocytic titer between prevaccination and postvaccination sera sampling.

| | Percentage of recipients | | | | Percentage of elderly recipients, per age group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Streptococcus pneumoniae* serotype | Young, aged 22–46 y ($n$ = 12) | | All elderly, aged 63–103 y ($n$ = 46) | | Group 1: 63–79 y ($n$ = 10) | | Group 2: 80–89 y ($n$ = 22) | | Group 3: ≥90 y ($n$ = 14) | |
| | ELISA | Opsono | ELISA | Opsono | ELISA | Opsono | ELISA | Opsono | ELISA | Opsono |
| 4 | 45 | 73 | 47 | 42 | 50 | 60 | 38 | 48 | 57 | 21* |
| 6B | 83 | 83 | 44* | 57 | 70 | 50 | 43* | 64 | 29* | 50 |
| 14 | 92 | 75 | 56* | 59 | 50 | 30 | 67 | 68 | 43* | 50 |
| 19F | 75 | 83 | 41 | 31* | 30 | 20* | 64 | 38* | 14* | 29* |
| 23F | 50 | 75 | 33 | 38* | 30 | 40 | 32 | 38 | 36 | 36 |

NOTE. Opsono = opsonophagocytosis.

* Significant difference ($P < .05$) between young controls and elderly groups, per Fisher's exact two-tailed test. Prevaccination IgG concentrations (μg/mL) in the elderly were significantly elevated only for serotype 14.

was a significant reduction in opsonophagocytic GMTs for the elderly ($P < .05$) when compared with GMTs for young adults (table 1). Differences in opsonophagocytic GMTs were more evident as age increased: in group 1, differences were significant only for serotype 19F; in group 2, for serotypes 4 and 6B; and in group 3, for all serotypes except 23F (figure 1B).

Prevaccination opsonophagocytic titers of all elderly recipients were also significantly lower for all serotypes, except serotype 23F, when compared with those for younger adults (table 1). A significantly lower percentage of elderly vaccine recipients than young controls attained a fourfold or higher rise in opsonophagocytic titers (after vaccination) for serotypes 4, 19F, and 23F (table 2).

Serum IgG antibody concentrations ($\log_2$) in elderly and young adults had significant ($P < .05$) correlation coefficients of association ($r$ values) with opsonophagocytic titers ($\log_2$) for all the serotypes tested (figure 2). However, postvaccination $r$ values for serotypes 4, 6B, 19F, and 23F were lower for sera from elderly persons ($r$ values ranged from .30 to .62) than for sera from young adults ($r$ values ranged from .61 to .86). This reduction in correlation coefficients was due to a higher number of serum specimens from elderly persons who had IgG antibody concentrations of ≥2 μg/mL and opsonophagocytic titers of <64. The proportion of sera with opsonophagocytic titers of ≥64, as well as IgG antibody concentrations of ≥2 μg/mL, was significantly reduced in most elderly groups for serotype 6B (21%–45% in the elderly groups vs. 92% in young adults), serotype 19F (30%–42% for elderly groups vs. 83% in young adults), and serotype 14 (36% in elderly group 3 vs. 83% in young adults). To determine reasons for the differences in functional antibody activity observed between elderly and young adults, we further analyzed these sera to assess antibody avidity measurements and passive protection in mice.

*Antibody avidity measurements.* For the avidity assays performed in sera from elderly persons with low opsonophagocytic activity, low concentrations of NaSCN (range, 0.005 $M$–0.15 $M$) were able to reduce ELISA optical density by 85% (SD, ±13.2%). This suggested that the antibody measured by ELISA was of low avidity. In 37 serum assays that showed a discrepancy between IgG antibody concentration and opsonophagocytic titer, 34 (92%) of the specimens had low antibody avidity. In contrast, in sera with anticapsular antibody of ≥2 μg/mL (threshold IgG concentration) and a high opsonophagocytic titer (≥64 threshold titer), the reaction between IgG antibody and type-specific PPS was significantly inhibited only by higher NaSCN concentrations (≥0.44 $M$), suggesting the presence of high-avidity antibody in the sera. Figure 3A shows a significant correlation ($r = .76$, $P < .01$) between opsonophagocytic titer ($\log_2$) and the weighted average of NaSCN concentration. There was a significant correlation between ELISA IgG antibody concentration and the weighted average of NaSCN concentrations ($r = .36$, $P < .01$), although the $r$ value was lower than that obtained with opsonophagocytosis (figure 3B). The association of low antibody avidity and low opsonophagocytic antibody activity was observed in sera from elderly and young adults.

*Passive protection in mice.* A high opsonophagocytic titer and high avidity for capsular PPS antigens were found to confer protection against pneumococcal challenge in mice. Thus, for example, serum 7023 (a specimen from an elderly subject that had high avidity and high opsonophagocytic activity) protected mice at all doses tested (table 3). In contrast, identical doses of IgG antibody from serum 7047, a specimen with low avidity and low opsonophagocytic activity from an elderly person, failed to protect even at the lowest inoculum of pneumococci. Sera with IgG antibody of intermediate avidity exhibited intermediate degrees of protection (data not shown). Because all sera tested had similar IgG antibody concentrations and yet conferred varying degrees of protection in mice, no association was observed between ELISA IgG antibody concentration and protection against death.

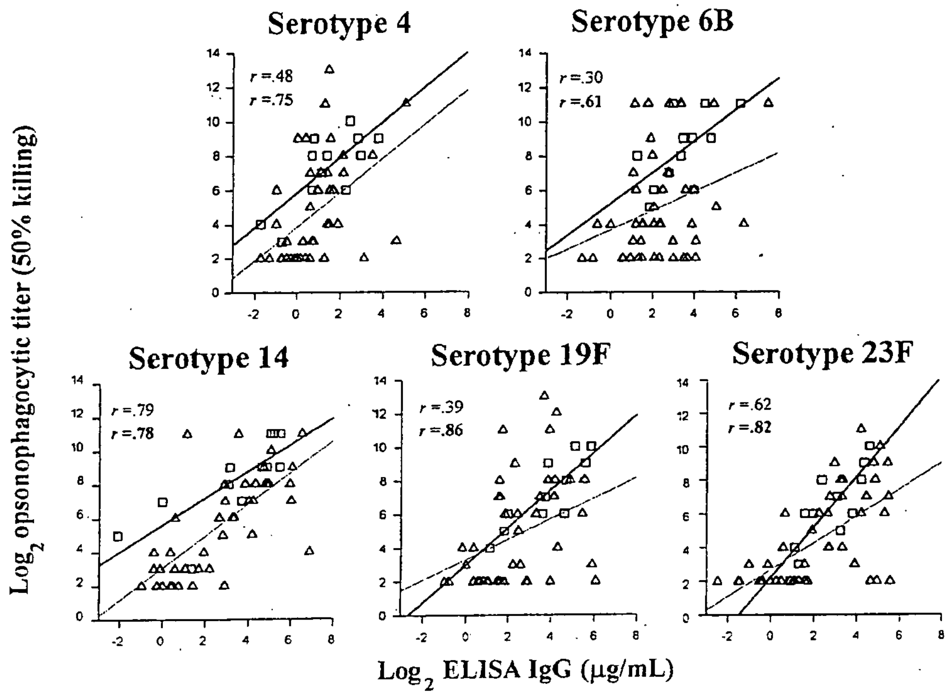


**Figure 2.** Correlation between $\log_2$ ELISA IgG antibody concentration (μg/mL) and $\log_2$ opsonophagocytic titer in postvaccination sera from young controls ($n$ = 12; *squares*) and elderly recipients of vaccine against *Streptococcus pneumoniae* serotypes 4, 6B, 14, 19F, and 23F ($n$ = 46; *triangles*). Linear regression for sera from young adults is indicated by the bold line, whereas the other line designates the linear regression for sera from elderly adults.

## Discussion

Our observations indicate that IgG antibody to PPSs is elicited in most elderly persons following vaccination. Similar percentages of elderly and young adults had IgG antibody at or above a threshold concentration of 2 μg/mL to four of the five PPSs tested. However, the IgG antibody GMCs were lower for two PPSs, and the ability to elicit twofold or higher increases in IgG antibody among the elderly was lower for two PPSs. This suggests that although responsiveness to polysaccharide antigens is retained with increasing age, it may be at a diminished level.

It is possible that the reduction observed in the elderly was due to the measurement of antibodies at 2–3 weeks instead of 4 weeks postvaccination. However, Musher et al. had previously shown only small differences in the IgG antibody concentration measured at 14 vs. 27 days postvaccination [12]. Earlier studies showed less [14] or no [12, 28] diminution in the antibody response with aging; differences in our results may reflect the fact that most of our elderly participants were >80 years of age. In addition, the predominance of women in our study group may have been a factor; Sankilampi et al. [14] found that women have slightly lower antibody responses to some pneumococcal polysaccharide antigens.

A more important finding of the present study was that the ability to elicit a functional antibody response is distinctly reduced with advanced age, as was shown by significantly lower opsonophagocytic GMCs in the elderly than in young adults to all the serotypes tested. This type of reduction was noticed in only ~20% of the elderly studied in a recent investigation by Rubins et al. [28]; however, only serotype 14 was assessed for functional antibody activity.

Our observations indicate that functional opsonophagocytic activity to serotype 14 highly correlates with ELISA IgG antibody concentrations (figure 2) and that PPS 14 elicits antibodies of higher avidity in both elderly and younger adults than do other PPSs commonly tested. Therefore, significant differences in functionality (opsonophagocytosis and/or antibody avidity) of the antibodies generated in the elderly may not be observed by studying only this serotype.

Our study suggests that the ability to elicit a fourfold or higher rise in opsonophagocytic antibody titers following vaccination decreased with age for three of the five serotypes tested. In addition, the number of elderly persons with an opsonophagocytic titer ⩾64 and an ELISA IgG antibody concentration ⩾2 μg/mL was lower for serotypes 6B and 19F, as well as for serotype 14 in the very elderly. For serotypes 4 and 23F the percentage of elderly recipients with high opsonophagocytic titers decreased, although not significantly (data not shown).

These observations were strengthened by the results of the

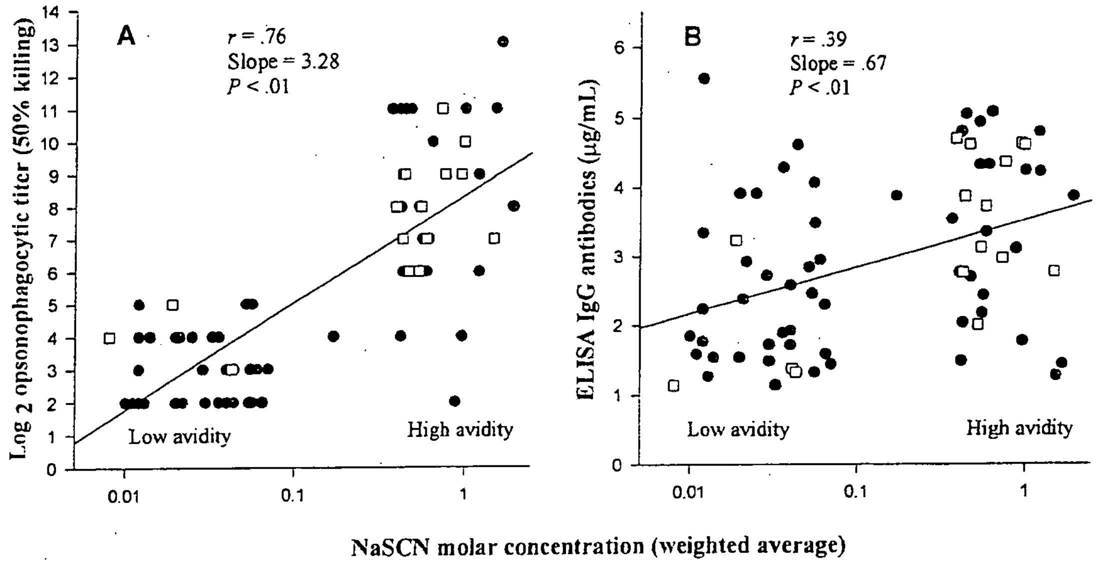


Figure 3. *A*, Correlation between the weighted average of the sodium thiocyanate (NaSCN) molar concentration yielding most of the reduction in ELISA IgG absorbance and the $\log_2$ opsonophagocytic titer. Results represent all serotypes (combined) in selected sera from elderly subjects (*black circles*) and young adults (*squares*). The line designates the linear regression. All sera with high antibody avidity also had high opsonophagocytic titers (⩾64), except for sera from three elderly subjects that were tested against *Streptococcus pneumoniae* serogroup 4 and had low opsonophagocytic titers (<64) and high antibody avidity (weighted averages: 0.42 *M*, 0.88 *M*, and 0.96 *M* NaSCN). All serum samples shown had ELISA IgG antibody concentrations ⩾2 µg/mL. *B*, Correlation between the weighted average of the NaSCN molar concentrations yielding most of the reduction in ELISA IgG absorbance and the ELISA IgG antibody concentration (µg/mL). Symbols are the same as in panel *A*. Sera with low antibody avidity (0.01 *M* to 0.1 *M* NaSCN) also had low opsonophagocytic titers (<64), regardless of the ELISA IgG antibody concentration. Sera with high antibody avidity (>0.4 *M* NaSCN) also had high opsonophagocytic titers (⩾64).

passive-protection experiments in mice with use of *S. pneumoniae* serotype 4, in which 100% protection was achieved by administering a serum with high opsonophagocytic titer and antibody avidity; no protection was observed with a serum that had low opsonophagocytic titer and antibody avidity. Similar patterns of passive protection were observed for serotype 6B with sera from elderly and young adults in an infant mouse model of bacteremia (data not shown).

Differences between IgG antibody measured by ELISA and functional opsonophagocytic activity in sera from elderly persons appeared to be related to differences in the avidity of IgG for PPS. Low concentrations of NaSCN readily inhibited the interaction between PPSs and IgG antibody from sera with low opsonophagocytic activity, whereas much higher concentrations of NaSCN were needed to produce such inhibition in sera with high opsonophagocytic activity, such as antibodies against serotype 14.

**Table 3.** Passive protection capacity of sera from elderly persons with known ELISA IgG antibody concentration, opsonophagocytic titer, and antibody avidity against *Streptococcus pneumoniae* serotype 4.

| Serum no. | Age (y) of patient | Dose of IgG antibody to serotype 4 (ng) | Percentage of mice surviving* after challenge with 10 × $LD_{50}$ | 100 × $LD_{50}$ | 1,000 × $LD_{50}$ | Opsonic titer (50% killing) | ELISA IgG (µg/mL) | Antibody avidity: NaSCN† |
|---|---|---|---|---|---|---|---|---|
| 7023 | 90 | 150 | 100 (4/4) | 100 (4/4) | 100 (4/4) | 8,192 | 2.7 | 1.67 |
| | | 50 | 100 (4/4) | 100 (4/4) | 100 (4/4) | | | |
| | | 18 | 100 (4/4) | 100 (4/4) | 100 (4/4) | | | |
| | | 6 | 100 (4/4) | 100 (4/4) | 100 (4/4) | | | |
| 7047 | 74 | 150 | 25 (1/4) | 0 (0/4) | 0 (0/4) | 4 | 2.4 | 0.013 |
| | | 50 | 50 (2/4) | 0 (0/4) | 0 (0/4) | | | |
| | | 18 | 50 (2/4) | 0 (0/4) | 0 (0/4) | | | |
| | | 6 | 0 (0/4) | 0 (0/4) | 0 (0/4) | | | |

NOTE. $LD_{50}$ = lethal dose for 50% of adult mice (1 $LD_{50}$ = 2–4 bacteria/mL).
* In parentheses is the no. of surviving mice/total no. of mice challenged.
† Molar concentration of sodium thyocyanate (NaSCN) necessary to yield an 85% reduction in ELISA IgG optical density.

In a study of older adults, Konradsen found no notable discrepancies between antibody concentration and avidity for various PPSs [29]; however, this finding may reflect the use of subjects 60–67 years of age, 20–40 years younger than the elderly subjects in our study. Similarly, Rubins et al. found no difference between elderly and younger adults in terms of serum antibody concentration and antibody avidity to serotype 14 [28]; however, as mentioned above, this serotype rarely elicits antibodies of low avidity in the elderly. Our study indicates that only nine of 46 elderly recipients had an opsonophagocytic titer <64 and an ELISA IgG antibody concentration ⩾2 μg/mL against PPS 14. Neither one of these studies made a direct correlation between opsonophagocytic activity and antibody avidity.

In the immunogenicity studies reported to date, the elderly have responded equally to conjugated and unconjugated polysaccharides [30, 31]; however, the functional antibody response has not been addressed in these studies. If the poor functionality of antibodies to PPSs as humans age is caused by an adherent accessory cell deficiency for antigenic presentation in the spleen, as has been shown in mice [32], a vaccination strategy may not be able to overcome the defect. Reduced neutrophil function in the elderly (reduced activation of superoxide anions and increased level of apoptosis) could account for the increased risk for pneumococcal infections, regardless of vaccination status [33, 34].

In summary, this study highlights the importance of evaluating the IgG antibody response, as well as the functional antibody activity of the antibodies measured, especially in high-risk populations. The distinct reduction in functional IgG antibody activity in the elderly was more pronounced in those 80–89 years of age and ⩾90 years of age. However, these age groups represent only 21% and 4.3%, respectively, of the target U.S. elderly population (32.4 million persons ⩾65 years old) for the pneumococcal polysaccharide vaccine [35].

Thus, this study should not discourage the use of the 23-valent polysaccharide vaccine in the elderly until a better vaccination strategy is available. New and improved approaches to vaccination in the elderly should be considered.

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